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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/685,343	10/11/00	CHARNEAU	P 03495.0197

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EXAMINER	
DRABIK,C	
ART UNIT	PAPER NUMBER
1633	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)	
	09/685,343	CHARNEAU ET AL.	
	Examiner	Art Unit	
	Christopher Drabik	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The response to the Restriction Requirement has been received and entered as paper NO 7. The applicants have chosen to elect HIV-1 as the species to be examined. Claim 4 has been withdrawn from prosecution because it is drawn to non-elected subject matter. The Restriction Requirement is made **FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites : "The process of claim 22, wherein the heterologous nucleic acid encodes..." Claim 22 further depends form claim 21. No antecedent basis exists in either claim 21 or 22 for the phrase "heterologous nucleic acid" recited in claim 22.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 21-28, 33-37 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10,21-28,33-37 and 38-40 encompass the in vivo transfer of genes intended to ameliorate or cure human disease states, hence the claims fall within the art of gene therapy. Claims 21- 28 are drawn to inserting a nucleic acid of interest into the nucleus of a target cell. These claims include both in vivo and in vitro uses. Claims 33-37 are drawn to a process for expressing a gene in vivo. Claims 38- 40 encompass a process for treating an individual pre-disposed or having a genetic disease or disorder. Claim 10 is a product claim which does not recite explicitly the use of the claimed nucleic acid for therapy, however, since the nucleic acid encodes a therapeutic protein, the nucleic acids' implicit use is for therapy. While Claims 21-28 do not recite specifically therapy as an intended use, the scope of Claims 21-28 encompass the use of the nucleic acid as a means for in vivo treatment, and hence the scope includes applications involving gene therapy.

As claims encompassing gene therapy these inventions are anticipatory of a treatment which alleviates a disease state. Gene therapy as a means for curing or alleviating human disease states remains incompletely proven and unpredictable. Verma et al. In reviewing the art of gene therapy writes: "Although more than two hundred clinical trials are currently underway... there is still no single outcome that we can point to as a success story" (see Verma et al (1997) Science 389: 239-242 see page 239, col. 1). More recently, Patterson, directing remarks to the Senate subcommittee on Public Health stated :"To date more than 4000 patients have

participated in gene therapy studies (in 372 NIH registered trials)... Only one percent of the trials (3 protocols) have progressed to phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety rather than efficacy. For this reason, it is perhaps more appropriate to refer to this technology as gene "transfer" rather than 'gene therapy', until there is more evidence for the therapeutic benefit of this technology." (Patterson A (2000) http://www4.od.nih.gov/oba/patterson2-00.pdf see page 2, 2nd full paragraph).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al Gene-Based Therapy in *The Pharmaceutical Basis of Therapeutics*, *9th ed* (1996) McGraw Hill ¶ bridging pages 81-82.]

The scope of claims 21-28, 33-37 and 38-40 also encompasses the specific ability to target cell types in vivo. A further aspect of the gene therapy which contributes to the unpredictability of gene therapy regards the ability of a given construct to target

specific cell types and in sufficient quantities to generate a therapeutic effect. Deonarain indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (Deonarian M P, (1998) Exp. Opin. Ther Patents 8: 53-69; see page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicates vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Regarding specifically gene therapy in the context of applications to cancer, the construction of vectors capable of specifically targeting cancer cells has been an elusive goal and remains a significant challenge to overcome. Vile in reviewing the field of cancer gene therapy comments"...efficiency and accuracy of gene delivery remain the most significant barriers to success. So far, there has been a disappointing inability to reach target cells with sufficient efficacy to generate high enough levels of direct killing..."(Vile et al (2000) Gene Therapy 7:2-8; see abstract) . In so far as the claims are drawn to therapeutic uses involving the in vivo viral vector targeting of cells the claims are not allowable based on the unpredictability in the art regarding cell targeting.

A further aspect of the instant invention regards ex vivo gene therapy. Ex vivo therapy suffers from some of the common shortcomings that in vivo vector delivery systems encounter. For example, the long term expression of a transferred gene is not a predictable outcome. Verma et al describe in vivo "transcriptional shutoff" of genes inserted ex vivo into cells using retroviral constructs (Verma page 240, 2nd column). Echoing Verma's point of view, Hanozono states "One major limitation to the use of retroviral vectors for gene therapy may be decline of expression of transgenes in vivo. The insertion of retroviral DNA can trigger transcriptional silencing of the inserted sequences..." (Hanozono et al (2001) Stem Cells 19:12-2, see page 16, 2nd column) While Verma et al overcame this problem through experimenting with transcriptional regulatory elements, the ability to determine the appropriate regulatory elements for all cell types remains "... a case of trial and error for a given type of cell." Hence, the construction of vectors effective for a specific ex vivo (or in vivo) application requires more than routine experimentation before a suitable combination is found. In a review regarding specifically ex vivo gene transfer to hematopoetic stem cells, Hanazono states "...very little clinical utility has been achieved in clinical trials in most of the HSC (human hematopoetic stem cell) gene therapy trials" and "...low gene transfer is still a problem that remains to be resolved for more widely applicable HSC gene therapy" (Hanazon et al, page 13, column 1). Verma et al further point out " [a]nother formidable challenge to the ex vivo approach is the efficiency of transplantation of the infected cells" (Verma et al page 240, 3rd column). Verma et al relate while long term expression of genes in a myoblast cell line were demonstrated in mice, similar

experiments in dogs led to only short term expression because the infected cells were incapable of fusing with muscle fibers. (2nd and 3rd columns). Hematopoeitic cells "may offer an advantage for ex vivo therapy ..." however,"...there is still a lack of a good enhancer-promoter combination that will allow sustained production of high levels of proteins in these cells" (Verma et al page 240, 3rd column).

While the claims are drawn to the in vivo and ex vivo treatment of human diseases states in involving the transfer and expression of therapeutic genes, the applicants have provided only examples of in vitro experimentation. The vector constructs are limited to HIV-1 derived vectors encoding a marker protein (GFP). The applicants have not demonstrated the in vivo production of any protein. Applicants have not demonstrated the construction of any sort of vector containing a therapeutic gene and have not shown that any vector as claimed would function in vivo for the expression of a therapeutic gene.

Based on the scope of the invention, the state of the prior art and the lack of working examples, the disclosure does not provide enablement for one of skill in the art to use the claimed nucleic acids and vectors for gene therapeutic purposes.

Claims 21-28 and 29-32 while being enabling for inserting a nucleic acid into the nucleus of a cell or expressing a gene in a cell in vitro wherein 1.) the nucleic acid sequence and/or gene comprises an HIV-1 derived vector 2.) the cells are within the host range of wild type HIV-1 or HIV-1 pseudotyped with VSV coat proteins and 3.) the size of the nucleic acid insert does not exceed 9 kb, the disclosure is not enabling for

the use of vectors other than HIV-based vectors, is not enabling for the transduction of cells not within the host range of HIV-1 or VSV pseudotyped HIV-1, is not enabling for the targeting of cells in vivo and is not enabling for nucleic acids which exceed the allowable insert size of an HIV-1 based vector. It should be further noted that Claims 21-28 encompass gene therapy and rejections based on this aspect of the scope of Claims 21-28 are addressed elsewhere in the Office Action.

Claims 21 –28 are drawn to a process of inserting a nucleic acid of interest into target cells, said process wherein the nucleic acid is a vector, wherein said nucleic acid encodes a heterologous nucleic acid, wherein said nucleic acid can encode a peptide, polypeptide, protein or therapeutic protein, wherein said target cell is a non-dividing-cell, HeLA cell or hematopoetic cell. The scope of claims 21-28 encompasses any nucleic acid containing the HIV-1 cPPT and CTS regions capable of transducing eukaryotic cells such that the nucleic acid is inserted into the nucleus of a target cell. The scope of Claims 21-28 encompasses any vector, any peptide, polypeptide or protein and further encompasses both in vitro and in vivo insertion of nucleic acids targeted to specific cell types. In addition to the reasons set forth above, these claims are not enabled for the reasons that follow.

Claims 29- 32 is drawn to a process for expressing a gene of interest in vitro wherein the process includes the use of a nucleic acid, said process encompasses the use of a vector and further comprises isolating the product of the expressed gene. The scope of the claims are the same as for claims 21-28 with the exception that in vivo expression of a gene of interest is not claimed.

The nature of Claims 21-28 and 29-32 involves the transformation of cell with an expression vector which encodes an allegedly enhanced nuclear localization signal. The nuclear localization signal is believed to derive from a secondary structure (triplex) formed in the cPPT/CTS region of HIV-1 DNA. (Post reverse transcription). Critical to the functioning of the invention as claimed is the generation of the triplex structure, which is based upon the reverse transcription of a nucleic acid . It is unclear and likely not possible that the triplex structure could be generated by other means. Hence, the claimed process must include a reverse transcription step. It has not been demonstrated that any other reverse transcriptase but that of HIV-1 will function to generate the HIV-1 cPPT/CTS directed triplex and, therefore a further limitation of the system appears to be that the process must involve HIV- 1 reverse transcriptase. This further delimits the claimed process to applications in which HIV-1 based vector systems are used for the transfer of nucleic acids or genes.

Based on the limitation of HIV-1 vector systems, the claims can only be enabled for cells which are within the host range of HIV-1 or cells which can be infected by pseudotyped HIV –1 viral particles. VSV has been demonstrated to work with the vector system as disclosed. It is unclear that the use of other methods of pseudotyping of HIV-1 within the context of the process of the instant application would function to expand the host range of the vector system.

The examples provided in the instant application include the construction of viral vectors based on HIV vectors described in Naldini et al. (Science (1996) 272:263-267).

The upper limit of gene insertion into this vector is approximately 9kb and therefore the functional limitation of inserted nucleic acid (or gene) is limited to 9kb.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 13 is drawn to a vector designated as pTRIP ΔU3 EF1αGFP. The construction of pTRIP ΔU3 EF1αGFP is described on pages 30-32 of the instant application, however, based on the disclosure, adequate description of the vector is not provided such that one of skill in the art could make and use the vector commensurate with the scope of the claims. The construction of the vector begins with the TRIP GFP plasmid (see page 30, line 12). However, the construction of TRIP GFP is not described and it is not apparent whether the TRIP GFP plasmid is readily available.

If strain(s) is not so obtainable or available, the requirements of 35 USC 112 may be satisfied by deposit thereof. The specification does not disclose a repeatable process to obtain the exact same strain(s) and it is not apparent that if such strain(s) are readily available to the public. If the deposit of the virus strain(s) is made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the strain(s) of will be irrevocably and without restriction or condition

released to the public upon issuance of a patent would satisfy the deposit requirements herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801 – 1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the viability of the biological material at the time of deposit will be tested (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-9, 11, 12, 14-25, 28-31, 41and 43 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Akkina et al (Journal of Virology (1996) 70:2581-2585)

Akkina et al disclose a recombinant HIV-1 vector which meet the limitations of claims 1-4, 6-9, 11, 12, 14-25, 28-31, 41 and 43.

Claims 1-4, 6 and 7 are drawn to an isolated nucleic acid comprising the cPPT and CTS regions of HIV-1 . Claim 8 is drawn to said nucleic acid also comprising a heterologous sequence. Claim 9 specifies that the heterologous nucleic acid is a peptide, polypeptide or a protein. Akkina et al disclose an HIV-1 based vector comprising the entire HIV-1 genome except for a deletion within the ENV gene. The vector also comprises the firefly luciferase gene(see page 2582, figure 1) Since the construct contains both the cPPT/ CTS regions (the vector contains the entire coding sequence of the pol gene as well as sequences 3' to the pol gene) and a heterologous sequence encoding a protein the limitations of Claims 1-4 and 6-8 are clearly anticipated. It should be further noted that the breadth of claims 1-4 and 6-8 encompass wild type HIV-1 and these claims are also anticipated by any disclosure of a complete HIV-1 nucleic acid

The vector disclosed in Akkina et al is an expression vector, coding for both HIV-1 proteins and firefly luciferase. The vector is described as being transfected into COS cells. Retroviral particles comprising the vector are used to infect several cell types including hematopoeitic progenitor cells (stem cells) (see page 2582 1st column and Table 1). Hence, the limitations of Claims 11,12, 14 and 18-20 are clearly anticipated.

Claim 15, 16 and 17 recite a virus, wherein the virus is a retrovirus or a lentivirus. The viral vector described in Akkina is a virus. The vector is derived from a lentivirus which is also a retrovirus. Hence claims 15-17 are clearly anticipated.

Claims 21 and 22 are drawn to a process for the insertion of a nucleic acid of interest into the nucleus of a cell wherein the nucleic acid comprises at least one copy of the HIV-1 cPPT and CTS regions. Claim 23 recites the nucleic acid is a vector. Claims 24 and 25 recite that the nucleic acid comprises a heterologous nucleic acid and that the heterologous nucleic acid encodes a peptide polypeptide or protein. Claims 29 –31 are drawn to a process for expressing a gene of interest in vitro utilizing a nucleic acid comprising the cPPT and CTS regions. The nucleic acids encompassed by the processes of claims 21-25 and 29-31 are anticipated by vector of Akkina et al (as set forth in the rejections for claims 11,12,14 and 18 above.) Akkina et al use the vector for the expression of viral and marker (luc) genes in several cell types, hence the process of in vitro expression of a gene of interest is clearly anticipated. Claims 21-25 and 29 – 31 are also anticipated by the expression of proteins by wild type HIV-1.

Claims 41 and 43 are drawn to a nucleic acid comprising the cPPT/CTS region of HIV-1. Claim 43 specifies that the nucleic acid is a vector. The critical limitations of these claims are also clearly anticipated by the HIV-1 vector disclosed by Akkina et al on page 2582 of their disclosure

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 24-26, 32 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akkina et al (Journal of Virology (1996) 70:2581-2585)

Claims 10 and 24-26, are drawn to nucleic acid constructs encoding heterologous nucleic acids, wherein the scope of the heterologous nucleic acid encompasses sequences encoding therapeutic proteins. Claim 27 is drawn to a process for inserting a nucleic acid into a target cell wherein the target cell is a non-dividing cell. Claim 32 is drawn to the purification or isolation of the proteins encoded by the heterologous sequence and claim 42 is drawn to a kit comprising a nucleic acid encoding the therapeutic protein.

The term "therapeutic protein" is broadly drawn and encompasses the proteins encoded by HIV-1. Therefore, the vector disclosed by Akkina et al encompass claims to a nucleic acid comprising therapeutic proteins and anticipates the limitations of claims 10, 24-26 and 42. An inherent property of lentiviral based vectors is the ability to infect non-dividing cells. A principal art utilized advantage of lentiviral vectors is there ability to infect non-dividing cells. Hence, the limitation of claim 27 is met by the disclosure of Akkina et al. In addition the vector disclosed by Akkina et al can be used for the isolation and purification of said therapeutic proteins by cell transfection and protein purification techniques widely known in the art. Any of the protein encoded for in the Akkina vector are of significant interest in the art of virology. Hence, the use of the vector for the production of these proteins would be obvious for one skilled in the art. In

addition, the replacement of luciferase protein by any other protein for expression and/or purification is an obvious aspect of the vector taught by Akkina and it would be apparent to one of skill in the art to utilize the vector in such a way.

Conclusion

No claim of the instant application is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

Deborah Clark

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